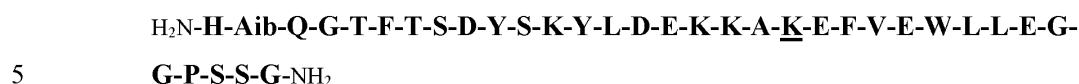


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CLAIMS:

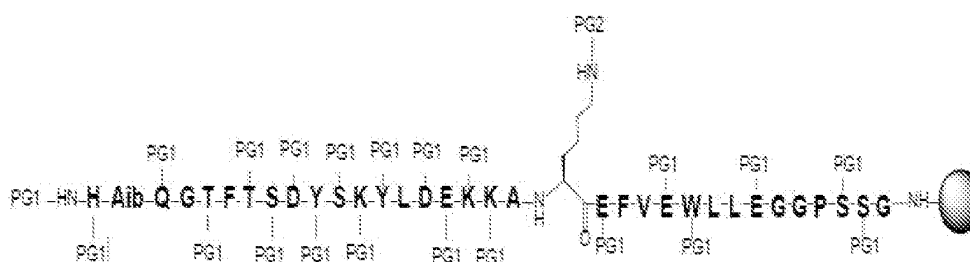
1. A process for the preparation of a compound of the following formula:



wherein Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with ([2-(2-aminoethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)₁₈CO₂H (SEQ ID NO: 1),

10 said process comprising the steps of:

- (i) solid-phase synthesis of a compound of the following formula



- 15 wherein PG1 is a base stable side-chain protecting group,
 wherein Thr at position 5 is optionally protected by PG1,
 and wherein PG2 is an ivDde, Dde or Alloc side-chain protecting group
 (SEQ ID NO: 2)
- 20 (ii) selectively acylating the compound at the Lys at position 20 (SEQ ID NO: 7) by selectively de-protecting said Lys and coupling the resulting Lys-NH₂ (SEQ ID NO: 5) with ^tBuO-C₂₀-γGlu(^tBu)-AEEA-AEEA-OH; and
- (iii) cleaving the acylated compound from the solid support and removal of the
 25 remaining side chain protecting groups; and

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- (iv) purifying the compound.
2. A process according to claim 1, wherein PG1 is:
- (a) Boc for Trp and Lys;
 - 5 (b) O^tBu for Asp and Glu;
 - (c) ^tBu for Ser, Thr and Tyr;
 - (d) Trt for Gln; and
 - (e) di-Boc for His.
- 10 3. A process according to claim 1 or claim 2, wherein PG2 is ivDde.
4. A process according to claim 1 or claim 2, wherein PG2 is Dde.
5. A process according to claim 3 or claim 4, wherein the Lys at position 20 is
15 selectively de-protected by reaction with a solution comprising hydrazine hydrate.
6. A process according to claim 5, wherein the solution comprises 1% - 15% w/w hydrazine hydrate in DMF, NMP, NBP or DMSO.
- 20 7. A process according to claim 5 or 6, wherein the solution comprises 8% w/w hydrazine hydrate in DMF.
8. A process according to claim 1 or claim 2, wherein PG2 is Alloc.
- 25 9. A process according to claim 5, wherein the Lys at position 20 is selectively de-protected by reaction with Pd(PPh₃)₄ in the presence of scavengers, preferably H₃N•BH₃, Me₂NH•BH₃, or PhSiH₃.
10. A process according to any one of claims 1-7, wherein PG1 is:
- 30 (a) Boc for Trp and Lys;
 - (b) O^tBu for Asp and Glu;

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- (c) ^tBu for Ser, Thr and Tyr;
 - (d) Trt for Gln; and
 - (e) di-Boc for His,
- wherein PG2 is ivDde,

5 wherein the solid-phase synthesis of the compound (SEQ ID NO: 3) of step (i) is performed on a Fmoc amide resin solid support and comprises Fmoc deprotection of the amide resin and sequential coupling of the following:

- (01) Fmoc-L-Gly-OH;
- 10 (02) Fmoc-L-Ser(^tBu)-OH;
- (03) Fmoc-L-Ser(^tBu)-OH;
- (04) Fmoc-L-Pro-OH;
- (05) Fmoc-L-Gly-OH;
- (06) Fmoc-L-Gly-OH;
- 15 (07) Fmoc-L-Glu(O^tBu)-OH;
- (08) Fmoc-L-Leu-OH;
- (09) Fmoc-L-Leu-OH;
- (10) Fmoc-L-Trp(Boc)-OH;
- (11) Fmoc-L-Glu(O^tBu)-OH;
- 20 (12) Fmoc-L-Val-OH;
- (13) Fmoc-L-Phe-OH;
- (14) Fmoc-L-Glu(O^tBu)-OH;
- (15) Fmoc-Lys(ivDde)-OH;
- (16) Fmoc-L-Ala-OH;
- 25 (17) Fmoc-L-Lys(Boc)-OH;
- (18) Fmoc-L-Lys(Boc)-OH;
- (19) Fmoc-L-Glu(O^tBu)-OH
- (20) Fmoc-L-Asp(O^tBu)-OH
- (21) Fmoc-L-Leu-OH;
- 30 (22) Fmoc-L-Tyr(^tBu)-OH;
- (23) Fmoc-L-Lys(Boc)-OH;

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- (24) Fmoc-L-Ser(^tBu)-OH;
(25) Fmoc-L-Tyr(^tBu)-OH;
(26) Fmoc-L-Asp(O^tBu)-OH;
(27) Fmoc-L-Ser(^tBu)-OH;
5 (28) Fmoc-L-Thr(^tBu)-OH;
(29) Fmoc-L-Phe-OH;
(30) Fmoc-Gly-Thr($\psi^{\text{Me,Me}}$ Pro)-OH;
(31) Fmoc-L-Gln(Trt)-OH;
(32) Fmoc-Aib-OH; and
10 (33) Boc-L-His(Boc)-OH.
11. A process according to any one of claims 1-7, wherein PG1 is:
- (a) Boc for Trp and Lys;
(b) O^tBu for Asp and Glu;
15 (c) ^tBu for Ser, Thr and Tyr;
(d) Trt for Gln; and
(e) Boc(Dnp) for His,
wherein PG2 is ivDde,
wherein the solid-phase synthesis of the compound (SEQ ID NO: 4) of
20 step (i) is performed on a Fmoc amide resin solid support and comprises Fmoc
deprotection of the amide resin and sequential coupling of the following:
- (01) Fmoc-L-Gly-OH;
(02) Fmoc-L-Ser(^tBu)-OH;
25 (03) Fmoc-L-Ser(^tBu)-OH;
(04) Fmoc-L-Pro-OH;
(05) Fmoc-L-Gly-OH;
(06) Fmoc-L-Gly-OH;
(07) Fmoc-L-Glu(O^tBu)-OH;
30 (08) Fmoc-L-Leu-OH;
(09) Fmoc-L-Leu-OH;

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- 5 (10) Fmoc-L-Trp(Boc)-OH;
 (11) Fmoc-L-Glu(O^tBu)-OH;
 (12) Fmoc-L-Val-OH;
 (13) Fmoc-L-Phe-OH;
 (14) Fmoc-L-Glu(O^tBu)-OH;
 (15) Fmoc-Lys(ivDde)-OH;
 (16) Fmoc-L-Ala-OH;
 (17) Fmoc-L-Lys(Boc)-OH;
 (18) Fmoc-L-Lys(Boc)-OH;
 10 (19) Fmoc-L-Glu(O^tBu)-OH
 (20) Fmoc-L-Asp(O^tBu)-OH
 (21) Fmoc-L-Leu-OH;
 (22) Fmoc-L-Tyr(^tBu)-OH;
 (23) Fmoc-L-Lys(Boc)-OH;
 15 (24) Fmoc-L-Ser(^tBu)-OH;
 (25) Fmoc-L-Tyr(^tBu)-OH;
 (26) Fmoc-L-Asp(O^tBu)-OH;
 (27) Fmoc-L-Ser(^tBu)-OH;
 (28) Fmoc-L-Thr(^tBu)-OH;
 20 (29) Fmoc-L-Phe-OH;
 (30) Boc-His(Dnp)-Aib-Gln(Trt)-Gly-Thr(^tBu)-OH.

12. A process according to any one of claims 1-7, wherein PG1 is:
- 25 (a) Boc for Trp and Lys;
 (b) O^tBu for Asp and Glu;
 (c) ^tBu for Ser, Thr and Tyr;
 (d) Trt for Gln; and
 (e) Boc(Dnp) for His,
 wherein PG2 is ivDde,

wherein the solid-phase synthesis of the compound (SEQ ID NO: 4) of step (i) is performed on a Fmoc amide resin solid support and comprises Fmoc deprotection of the amide resin and sequential coupling of the following:

- | | |
|----|--|
| 5 | (01) Fmoc-L-Gly-OH; |
| | (02) Fmoc-L-Ser(^t Bu)-OH; |
| | (03) Fmoc-L-Ser(^t Bu)-OH; |
| | (04) Fmoc-L-Pro-OH; |
| | (05) Fmoc-L-Gly-OH; |
| 10 | (06) Fmoc-L-Gly-OH; |
| | (07) Fmoc-L-Glu(O ^t Bu)-OH; |
| | (08) Fmoc-L-Leu-OH; |
| | (09) Fmoc-L-Leu-OH; |
| | (10) Fmoc-L-Trp(Boc)-OH; |
| 15 | (11) Fmoc-L-Glu(O ^t Bu)-OH; |
| | (12) Fmoc-L-Val-OH; |
| | (13) Fmoc-L-Phe-OH; |
| | (14) Fmoc-L-Glu(O ^t Bu)-OH; |
| | (15) Fmoc-Lys(ivDde)-OH; |
| 20 | (16) Fmoc-L-Ala-OH; |
| | (17) Fmoc-L-Lys(Boc)-OH; |
| | (18) Fmoc-L-Lys(Boc)-OH; |
| | (19) Fmoc-L-Glu(O ^t Bu)-OH |
| | (20) Fmoc-L-Asp(O ^t Bu)-OH |
| 25 | (21) Fmoc-L-Leu-OH; |
| | (22) Fmoc-L-Tyr(^t Bu)-OH; |
| | (23) Fmoc-L-Lys(Boc)-OH; |
| | (24) Fmoc-L-Ser(^t Bu)-OH; |
| | (25) Fmoc-L-Tyr(^t Bu)-OH; |
| 30 | (26) Fmoc-L-Asp(O ^t Bu)-OH; |
| | (27) Fmoc-L-Ser(^t Bu)-OH; |

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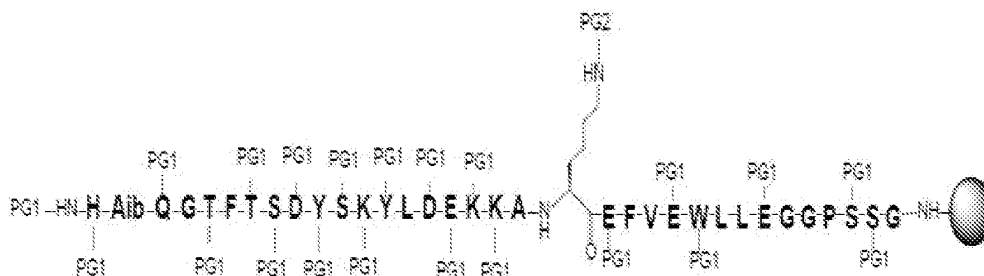
- (28) Fmoc-L-Thr(^tBu)-OH;
- (29) Fmoc-L-Phe-OH;
- (30) Fmoc-L-Thr(^tBu)-OH; and
- (31) Boc-His(Dnp)-Aib-Gln(Trt)-Gly-OH.

5

- 13. A process according to any one of claims 10-12, wherein the resin solid support is a Fmoc amide resin solid support and the solid phase synthesis comprises Fmoc deprotection of the resin.
- 10 14. A process according to claim 13, wherein the Fmoc amide resin solid support is a Sieber resin.
- 15. A process according to any one of claims 1-14, wherein step (iii) further comprises adjusting the pH of a solution comprising the cleaved and deprotected
15 compound to 7.0 – 8.0, stirring for 1-24 hours, subsequently adjusting the pH of the solution to 1.0 - 3.0, and stirring for 1-24 hours.
- 16. A process according to any one of claims 1-15, wherein the purification of the compound comprises subjecting the compound produced by step (iii) to
20 chromatographic purification.
- 17. A process according to claim 16, wherein the chromatographic purification is HPLC or reverse phase HPLC.
- 25 18. A process according to claim 16 or claim 17 wherein the purification further comprises the steps of (i) adding the chromatographic eluent to a solution comprising aqueous sodium hydroxide or aqueous sodium bicarbonate to form a sodium salt of the compound in solution, (ii) precipitating the sodium salt of the compound from solution and (iii) filtering, washing and drying the precipitated
30 sodium salt of the compound.

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19. A process for the preparation of a compound of the following formula:

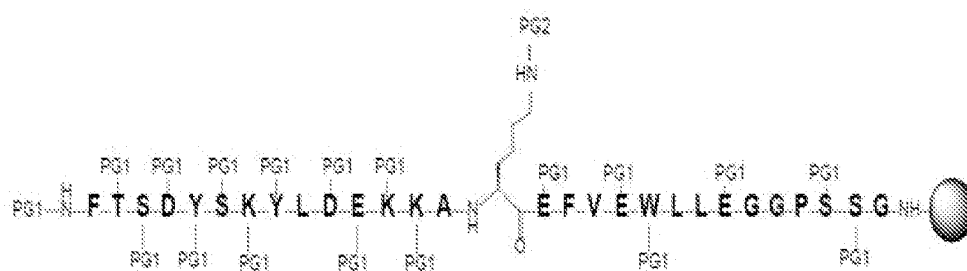


wherein PG1 is a base stable side-chain protecting group,

- 5 wherein PG2 is an ivDde, Dde or Alloc side-chain protecting group (SEQ ID NO: 17),

and wherein said process comprises the steps of:

- (i) solid-phase synthesis of a compound of the following formula:



10

wherein PG1 is a base stable side-chain protecting group,

and wherein PG2 is an ivDde, Dde or Alloc side-chain protecting group (SEQ ID NO: 9); and

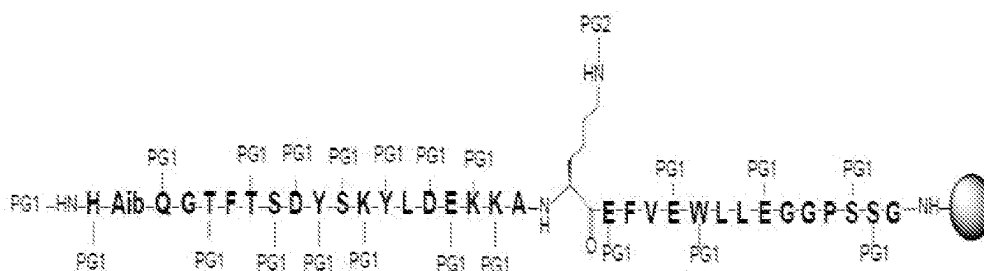
- 15 (ii) coupling the compound of step (i) with a pentamer of the following formula:

PG1-His(PG1)-Aib-Gln(PG1)-Gly-Thr(PG1)-OH

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wherein PG1 is a base stable side-chain protecting group (SEQ ID NO: 13).

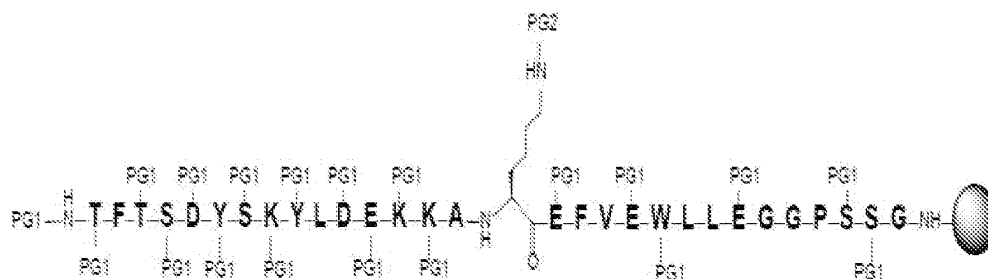
20. A process according to claim 19, wherein PG1 is
- 5 (a) Boc for Trp and Lys;
- (b) O^tBu for Asp and Glu;
- (c) ^tBu for Ser, Thr and Tyr;
- (d) Trt for Gln; and
- (e) Boc(Dnp) for His.
- 10 21. A process according to claim 19 or claim 20, wherein PG2 is ivDde.
22. A process according to claim 19 or claim 20, wherein PG2 is Dde.
- 15 23. A process for the preparation of a compound of the following formula:



wherein PG1 is a base stable side-chain protecting group,
 wherein PG2 is an ivDde, Dde or Alloc side-chain protecting group (SEQ ID NO:
 17),
 and wherein said process comprises the steps of:

- (i) solid-phase synthesis of a compound of the following formula:

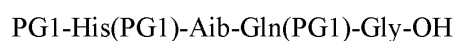
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wherein PG1 is a base stable side-chain protecting group,
and wherein PG2 is an ivDde, Dde or Alloc side-chain protecting group
(SEQ ID NO: 11); and

5

- (ii) coupling the compound of step (i) with a tetramer of the following
formula:



10

wherein PG1 is a base stable side-chain protecting group (SEQ ID NO:
15).

24. A process according to claim 23, wherein P is

- 15 (a) Boc for Trp and Lys;
(b) O^tBu for Asp and Glu;
(c) ^tBu for Ser, Thr and Tyr;
(d) Trt for Gln; and
(e) Boc(Dnp) for His.

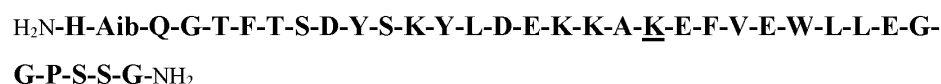
20

25. A process according to claim 23 or claim 24, wherein PG2 is ivDde.

26. A process according to claim 23 or claim 24, wherein PG2 is Dde.

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27. A process for the preparation of a sodium salt of the compound of the following formula:

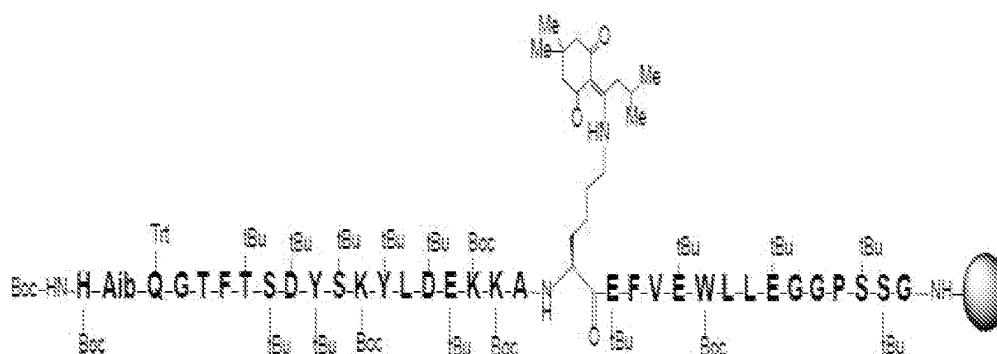


wherein lysine (Lys/K) at position 20 is chemically modified by conjugation of the epsilon-amino group of the lysine side chain with ([2-(2-aminoethoxy)-ethoxy]-acetyl)₂-(γ -Glu)-CO-(CH₂)₁₈CO₂H (SEQ ID NO: 1)

said process comprising the steps of:

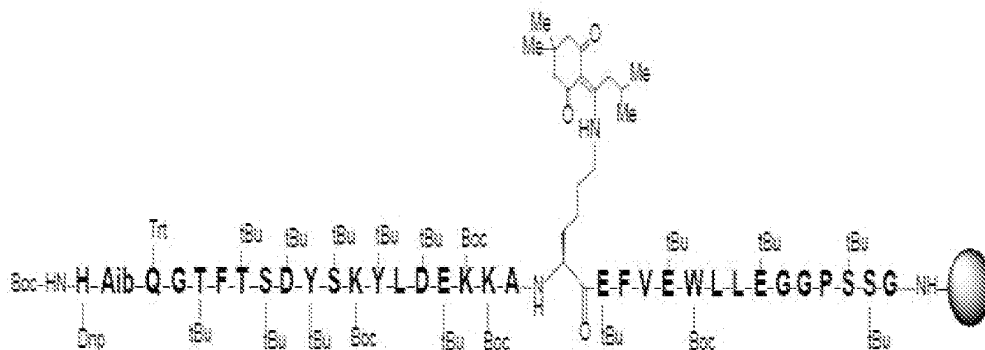
- (i) adding aqueous sodium hydroxide or aqueous sodium bicarbonate to a solution comprising the compound of SEQ ID NO: 1 to form a sodium salt of the compound in solution;
- (ii) precipitating the sodium salt of the compound from solution; and
- (iii) filtering, washing and drying the precipitated sodium salt of the compound of SEQ ID NO: 1.

28. A compound having the following formula (SEQ ID NO: 3):

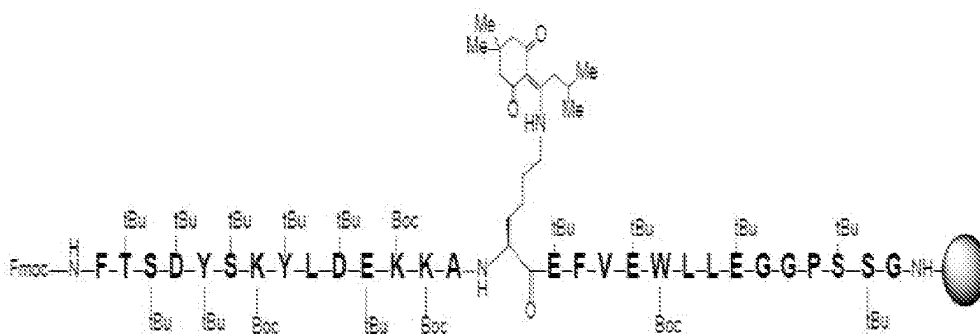


29. A compound having the following formula (SEQ ID NO: 4):

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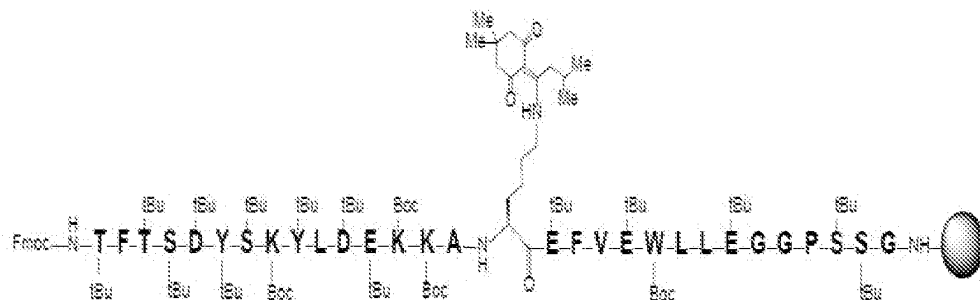


30. A compound having the following formula (SEQ ID NO: 10):



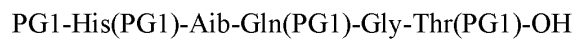
5

31. A compound having the following formula (SEQ ID NO: 12):



- 10 32. A compound having the following formula (SEQ ID NO: 13):

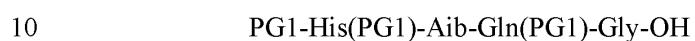
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wherein PG1 is a base stable side-chain protecting group.

- 5 33. A compound according to claim 32, wherein PG1 is ^tBu for Thr, Trt for Gln, and Boc(Dnp) for His..

34. A compound having the following formula (SEQ ID NO: 15):



wherein PG1 is a base stable side-chain protecting group.

35. A compound according to claim 34, wherein PG1 is Trt for Gln and Boc(Dnp) for
15 His.